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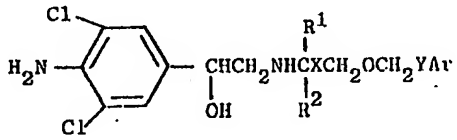
(54) Dichloroaniline derivatives

(57) The invention provides compounds of the general formual (I)



(I)

wherein
X represents a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain and
Y represents a bond, or a C_{1-4} alkylene, C_{2-4} alkenylene of C_{2-4} alkynylene chain with the proviso that the sum total of carbon atoms in X and Y is not more than 8; Ar represents a phenyl group optionally substituted by one or more substituents selected from halogen atoms, or the groups C_{1-3} alkyl, C_{1-3} alkoxy, $-(CH_2)_qOH$ (where q represents an integer from 0 to 3), $-NR^3R^4$ (where R^3 and R^4 each represents a hydrogen atom, or a C_{1-4} alkyl group, or NR^3R^4 forms a saturated heterocyclic amino group which has 5-7 ring members and optionally contains in the ring one or more atoms selected from $-O-$ or $-S-$ or a group $-NH-$ or $-N(CH_3)-$), or $-NR^5COR^6$ (where R^5 represents a hydrogen atom or a C_{1-4} alkyl group, and R^6 represents a hydrogen atom or a C_{1-4} alkyl, C_{1-4} alkoxy, phenyl or $-NR^3R^4$ group), or Ar as a phenyl group may be substituted by an alkylenedioxy group of formula $-O(CH_2)_pO-$, where p is 1 or 2; R^1 and R^2 each represents a hydrogen atom or a C_{1-3} alkyl group, with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4; and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

The compounds of formula (I) have a selective stimulent action at β_2-adrenoreceptors and are useful, in particular, in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

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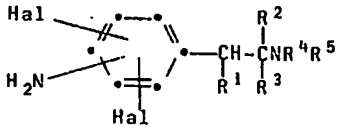
SPECIFICATION

Dichloroaniline derivatives

This invention relates to dichloroaniline derivatives having a stimulant action at β_2-adrenoreceptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Dihaloaniline derivatives have previously been described as bronchodilators having stimulant activity at β-adrenoreceptors.

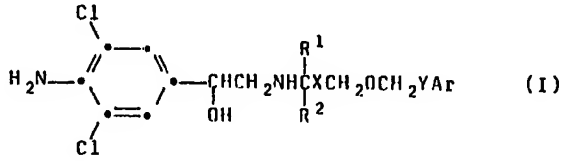
Thus British Patent Specification No. 1178191 describes compounds of the general structure



in which the substituents Hal represent bromine or chlorine atoms; R^1 represents hydrogen or hydroxyl; R^2 and R^3 each represent hydrogen or C_{1-4} alkyl; and R^4 and R^5 each represent hydrogen, C_{1-6} alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, dialkylaminoalkyl, cycloalkyl, phenyl, benzyl or adamantyl, or NR^4R^5 forms a heterocylic ring optionally substituted by C_{1-3} alkyl groups.

We have now found a novel group of dichloroaniline derivatives, which differ structurally from those described in British Patent Specification No. 1178191, and which have a desirable and useful profile of activity.

Thus the present invention provides compounds of the general formula (I)



(I)

wherein

X represents a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain and

Y represents a bond, or a C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene chain with the proviso that the sum total of carbon atoms in X and Y is not more than 8;

Ar represents a phenyl group optionally substituted by one or more substituents selected from halogen atoms, or the groups C_{1-3} alkyl, C_{1-3} alkoxy, $-(CH_2)_qOH$ (where q represents an integer from 0 to 3), $-NR^3R^4$ (where R^3 and R^4 each represents a hydrogen atom, or a C_{1-4} alkyl group, or NR^3R^4 forms a saturated heterocyclic amino group which has 5-7 ring members and optionally contains in the ring one or more atoms selected from $-O-$ or $-S-$ or a group $-NH-$ or $-N(CH_3)-$), or $-NR^5COR^6$ (where R^5 represents a hydrogen atom or a C_{1-4} alkyl group, and R^6 represents a hydrogen atom or a C_{1-4} alkyl, C_{1-4} alkoxy, phenyl or $-NR^3R^4$ group), or Ar is a phenyl group substituted by an alkylenedioxy group of formula $-O(CH_2)_pO-$, where p is 1 or 2;

R^1 and R^2 each represents a hydrogen atom or a C_{1-3} alkyl group, with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4; and

physiologically acceptable salts and solvates (e.g. hydrates) thereof.

It will be appreciated that the compounds of general formula (I) possess one or two asymmetric carbon atoms, namely the carbon atom of the

group and, when R^1 and R^2 are different groups, the carbon atom to which these are attached.

The compounds according to the invention thus include all enantiomers, diastereoisomers and mixtures thereof, including racemates. Compounds in which the carbon atom in the

group is in the R configuration are preferred.

In the definition of general formula (I), the term alkenylene includes both *cis* and *trans* structures.

In one aspect, the invention provides compounds of formula (I) in which R^1, R^2, Ar and Y are as defined in formula (I) and X represents a C_{2-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain.

In the general formula (I), the chain X may be for example $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2C\equiv C-$, $-(CH_2)_2CH=CH-$, $-(CH_2)_2C\equiv C-$, $-CH=CHCH_2-$, $-CH=CH(CH_2)_2-$ or

$-CH_2C{\equiv}CCH_2-$. The chain Y may be for example $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH{=}CH-$, $-C{\equiv}C-$, $CH_2CH{=}CH-$, or $-CH_2C{\equiv}C-$.

Preferably the total number of carbon atoms in the chains X and Y is 4 to 8 inclusive. Compounds wherein the sum total of carbon atoms in the chains X and Y is 4, 5, 6 or 7 are particularly preferred.

In one preferred group of compounds of formula (I) X represents a C_{2-6} alkynylene or, more preferably, a C_{2-6} alkylene chain and Y represents a C_{1-4} alkylene chain. Particular compounds of this type are those werein X is $-(CH_2)_3-$ or $-(CH_2)_4-$ and Y is $-CH_2-$, $-(CH_2)_2-$ or $-(CH_2)_3-$, or X is $-CH_2C{\equiv}C-$ and Y is $-CH_2-$.

In the compounds of formula (I) R^1 and R^2 may each be, for example, methyl, ethyl, propyl or isopropyl groups except that if one of R^1 and R^2 is a propyl or isopropyl group, the other is a hydrogen atom or a methyl group. Thus for example R^1 may be a hydrogen atom or a methyl, ethyl or propyl group. R^2 may be, for example, a hydrogen atom or a methyl group. R^1 and R^2 are each preferably a hydrogen atom or a methyl group.

A preferred group of compounds are those wherein R^1 and R^2 are both hydrogen atoms, or R^1 is a hydrogen atom and R^2 is a C_{1-3} alkyl group, particularly a methyl group.

When $-NR^3R^4$ in compounds of formula (I) represents a saturated heterocyclic amino group, this may have 5, 6 or 7 ring members and optionally contains in the ring a heteroatom selected from $-O-$ or $-S-$, or a group $-NH-$ or $-N(CH_3)-$. Examples of such $-NR^3R^4$ groups are pyrrolidino, piperidino, hexamethyleneimino, piperazino, N-methylpiperazino, morpholino, homomorpholino or thiamorpholino.

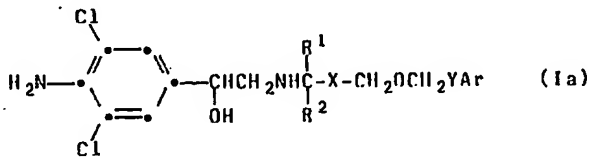
Ar may be for example a phenyl group. Examples of the optional substituents which may be present on the phenyl group represented by Ar include bromine, iodine, chlorine, fluorine, methyl, ethyl, methoxy, ethoxy, amino, methylamino, ethylamino, dimethylamino, diethylamino, morpholino, piperidino, piperazino, N-methylpiperazino, $-NHCOR^6$ [where R^6 is hydrogen, C_{1-4} alkyl, (e.g. methyl, ethyl, isopropyl or n-butyl), C_{1-4} alkoxy (e.g. methoxy, ethoxy, isopropoxy or n-butoxy), phenyl or amino], hydroxyl, $-CH_2OH$, or $-(CH_2)_2OH$.

The phenyl group represented by Ar may optionally contain one, two or three substituents, which may be present at the 2-, 3-, 4-, 5- or 6-positions on the phenyl ring.

Particular examples of a disubstituted phenyl group represented by Ar include phenyl substituted by two hydroxyl groups [e.g. 3,5-dihydroxyphenyl], or a hydroxyl and a methoxy group [e.g. 3-methoxy-4-hydroxyphenyl].

Particular examples of a trisubstituted phenyl group represented by Ar include phenyl substituted by an amino and two methyl groups [e.g. 3,5-dimethyl-4-aminophenyl], an amino group and two chlorine atoms [e.g. 3,5-dichloro-4-aminophenyl], or three methoxy groups [e.g. 3,4,5-trimethoxyphenyl].

A preferred group of compounds are those of the formula (Ia)



(Ia)

wherein

X represents a C_{3-4} alkylene or C_3 alkynylene chain;

Y represents a C_{1-3} alkylene chain;

R^1 and R^2 each represent hydrogen or methyl; and

Ar represents a phenyl group optionally substituted by a fluorine atom, a group selected from amino, C_{1-3} alkyl (e.g. methyl), C_{1-3} alkoxy (e.g. methoxy), hydroxy C_{1-2} alkyl (e.g. hydroxymethyl), morpholino, hydroxy or $-NHCOR^6$ where R^6 is C_{1-3} alkyl (e.g. methyl), or Ar is a phenyl group substituted by hydroxyl groups at the 3- and 5- positions; and physiologically acceptable salts and solvates thereof.

A particularly preferred group of compounds of formula (Ia) are those wherein Ar is a phenyl group optionally containing one substituent, more preferably an amino, $-NHAcetyl$ or morpholino group.

Particularly important compounds of the invention are:
4-amino-3,5-dichloro-α-[[[6-[2-[4-(4-morpholinyl)phenyl]ethoxy]hexyl]amino]methyl]benzenemethanol;
N-[4-[2-[[6-[[2-(4-amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]hexyl]oxy]ethyl]phenyl]acetamide;
4-amino-3,5-dichloro-α-[[[6-[2-(4-aminophenyl)ethoxy]hexyl]amino]methyl]benzenemethanol;
4-amino-3,5-dichloro-α-[[[5-(2-phenylethoxy)pentyl]amino]methyl]benzenemethanol;
4-amino-3,5-dichloro-α-[[[6-(2-phenylethoxy)hexyl]amino]methyl]benzenemethanol;
4-amino-3,5-dichloro-α-[[[1-methyl-5-(2-phenylethoxy)pentyl]amino]methyl]benzenemethanol;
4-amino-3,5-dichloro-α-[[[5-(2-phenylethoxy)-3-pentynyl]amino]methyl]benzenemethanol;
[3-[[5-[[2-(4-amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]pentyl]oxy]propyl]-1,3-benzenediol; and the physiologically acceptable salts and solvates thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-methoxybenzoates, 2- or 4-hydroxybenzoates, 4-chlorobenzoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, salicylates, ace-

tates, fumarates, succinates, lactates, glutarates, gluconates, tricarballylates, hydroxy-naphthalenecarboxylates e.g. 1-hydroxy- or 3-hydroxy-2-naphthalenecarboxylates, or oleates. The compounds may also form salts with suitable bases. Examples of such salts are alkali metal (e.g. sodium and potassium), and alkaline earth metal (e.g. calcium or magnesium) salts.

The compounds according to the invention have a stimulant action at β_2-adrenoreceptors, which furthermore is of a particularly advantageous profile. The stimulant action was demonstrated in the isolated trachea of the guinea-pig, where compounds were shown to cause relaxation of PGF2α-induced contractions. Compounds according to the invention have shown a particularly long duration of action in this test.

The compounds according to the invention may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

The compounds according to the invention are also indicated as useful for the treatment of inflammatory and allergic skin diseases, congestive heart failure, depression, premature labour, glaucoma, and in the treatment of conditions in which there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

The invention accordingly further provides compounds of formula (I) and their physiologically acceptable salts and solvates for use in the therapy or prophylaxis of diseases associated with reversible airways obstruction in human or animal subjects.

The compounds according to the invention may be formulated for administration in any convenient way. The invention therefore includes within its scope pharmaceutical compositions comprising at least one compound of formula (I) or a physiologically acceptable salt or solvate thereof formulated for use in human or veterinary medicine. Such compositions may be presented for use with physiologically acceptable carriers or excipients, optionally with supplementary medicinal agents.

The compounds may be formulated in a form suitable for administration by inhalation or insufflation, or for oral, buccal, parenteral, topical (including nasal) or rectal administration. Administration by inhalation or insufflation is preferred.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in for example capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For buccal administration the composition may take the form of tablets, drops or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For topical administration the pharmaceutical composition may take the form of ointments, lotions or creams formulated in a conventional manner, with for example an aqueous or oily base, generally with the addition of suitable thickening agents and/or solvents. For nasal application, the composition may take the form of a spray, formulated for example as an aqueous solution or suspension or as an aerosol with the use of a suitable propellant.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Where pharmaceutical compositions are described above for oral, buccal, rectal or topical administration, these may be presented in a conventional manner associated with controlled release forms.

A proposed daily dosage of active compound for the treatment of man is 0.005mg to 100mg, which may be conveniently administered in one or two doses. The precise dose employed will of course depend on the age and condition of the patient and on the route of administration. Thus a suitable dose for administration by inhalation is 0.005mg to 20mg, for oral administration is 0.02mg to 100mg, and for parenteral administration is 0.01mg to 2mg for administration by bolus injection and 0.01mg to 25mg for administration by infusion.

The compounds according to the invention may be prepared by a number of processes, as described in the following wherein X, Y, Ar, R^1 and R^2 are as defined for general formula (I) unless otherwise specified. It will be appreciated that certain of the reactions described below are capable of affecting other groups in the starting material which are desired in the end product; this applies especially in the reduction processes

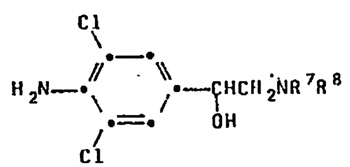
described, particularly were hydrogen and a catalyst are used and when an ethylene or acetylene linkage is required in the compound of the invention. Care must therefore be taken in accordance with conventional practice, either to use reagents which will not affect such groups, or to perform the reaction as part of a sequence which avoids their use when such groups are present in the starting material.

In the preparation of both intermediates and end-products the final step in the reaction may be the removal of a protecting group. Conventional protecting groups may be used, as described for example in "Protective Groups in Organic Chemistry", Ed. J. F. W. McOmie (Plenum Press, 1973). Thus hydroxyl groups may for example be protected by aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl, or as tetrahydropyranyl derivatives. Suitable amino protecting groups include aralkyl groups such as benzyl, α-methylbenzyl, diphenylmethyl or triphenylmethyl, and acyl groups such as acetyl, trichloroacetyl or trifluoroacetyl.

Conventional methods of deprotection may be used. Thus for example aralkyl groups may be removed by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal). Tetrahydropyranyl groups may be cleaved by hydrolysis under acidic conditions. Acyl groups may be removed by hydrolysis with a base such as sodium hydroxide or potassium carbonate, or a group such as trichloroacetyl may be removed by reduction with, for example, zinc and acetic acid.

In one general process (1), a compound of general formula (I) may be prepared by alkylation. Conventional alkylation procedures may be used.

Thus, for example, in one process (a), a compound of general formula (I) in which R^1 is a hydrogen atom may be prepared by alkylation of an amine of general formula (II)



(II)

(wherein R^7 is a hydrogen atom or a protecting group and R^8 is a hydrogen atom) followed by removal of any protecting group where present.

The alkylation (a) may be effected using an alkylating agent of general formula (III):

$$\underset{\displaystyle R^2}{\underset{|}{LCH}}XCH_2OCH_2YAr \qquad (III)$$

(wherein L is a leaving group, for example a halogen atom such as chlorine, bromine or iodine, or a hydrocarbylsulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonloxy).

The alkylation is preferably effected in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, organic bases such as triethylamine, diisopropylethylamine or pyridine, or alkylene oxides such as ethylene oxide or propylene oxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran or dioxan, a ketone e.g. butanone or methyl isobutyl ketone, a substituted amide e.g. dimethylformamide or a chlorinated hydrocarbon e.g. chloroform at a temperature between ambient and the reflux temperature of the solvent.

According to another example (b) of an alkylation process, a compound of general formula (I) in which R^1 represents a hydrogen atom may be prepared by alkylation of an amine of general formula (II), as previously defined except that R^8 is a hydrogen atom or a group convertible thereto under the reaction conditions, with a compound of general formula (IV):

$$R^2COXCH_2OCH_2YAr \qquad (IV)$$

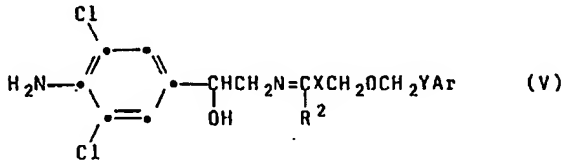
in the presence of a reducing agent, followed when necessary by removal of any protecting groups.

Examples of suitable R^8 groups convertible into a hydrogen atom are arylmethyl groups such as benzyl, α-methylbenzyl and benzhydryl.

Suitable reducing agents include hydrogen in the presence of a catalyst such as platinum, platinum oxide, palladium, palladium oxide, Raney nickel or rhodium, on a support such as charcoal, using an alcohol, e.g. ethanol or methanol, or an ester e.g. ethyl acetate, or an ether e.g. tetrahydrofuran, or water, as reaction solvent, or a mixture of solvents, e.g. a mixture of two or more of those just described at normal or elevated temperature and pressure, for example from 20 to 100°C and from 1 to 10 atmospheres.

Alternatively when one or both of R^7 and R^8 are hydrogen atoms, the reducing agent may be a hydride such as diborane or a metal hydride such as sodium borohydride, sodium cyanoborohydride or lithium aluminium hydride. Suitable solvents for the reaction with these reducing agents will depend on the particular hydride used, but will include alcohols such as methanol or ethanol, or ethers such as diethyl ether or *tert*-butyl methyl ether, or tetrahydrofuran.

When a compound of formula (II) where R^7 and R^8 are each hydrogen atoms is used, the intermediate imine of formula (V) may be formed:

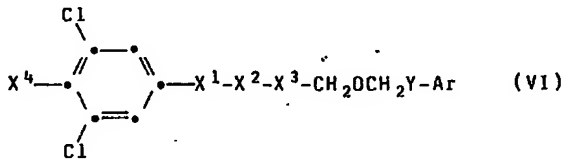


(V)

Reduction of the imine using the conditions described above, followed, where necessary, by removal of any protecting groups, gives a compound of general formula (I).

Where it is desired to use a protected intermediate of general formula (II) it is particularly convenient to use hydrogen and a catalyst as described above with protecting groups R^7 which are capable of being converted to a hydrogen atom under these reducing conditions, thus avoiding the need for a separate deprotection step. Suitable protecting groups of this type include arylmethyl groups such as benzyl, benzhydryl and α-methylbenzyl.

In another general process (2), a compound of general formula (I) may be prepared by reduction. Thus, for example, a compound of general formula (I) may be prepared by reducing an intermediate of general formula (VI):



(VI)

wherein at least one of X^4, X^1, X^2, X^3 and Y represents a reducible group and/or Ar contains a reducible group and the other(s) take the appropriate meaning as follows, which is X^4 is $-NH_2$, X^1 is $-CH(OH)-$, X^2 is $-CH_2NR^7-$ and X^3 is $-CR^1R^2X$, followed where necessary by removal of any protecting groups.

Suitable reducible groups include those wherein X^4 is $-NO_2$, X^1 is a group $-C=O$, X^2 is a group $-CH_2NY'-$ (wherein Y' represents a group convertible to hydrogen by catalytic hydrogenation, for example an arylmethyl group such as benzyl, benzhydryl or α-methylbenzyl), or an imine ($-CH=N-$) group or a group $-CONH-$, X^3 is a group $-COX-$ or a group CR^1R^2X (where X is C_{2-6} alkenylene or C_{2-6} alkynylene), or $-X^2-X^3-$ is a group $-CH_2N=CR^2X-$, Y is C_{2-4} alkenylene or alkynylene, and Ar is a phenyl group substituted by a nitro group or by a group $-CHO$ or $-CO_2R^9$ where R^9 is hydrogen or an alkyl (e.g. C_{1-3} alkyl) group.

The reduction may be effected using reducing agents conveniently employed for the reduction of carboxylic acids, aldehydes, esters, ketones, imines, amides, protected amines, alkenes, alkynes and nitro groups. Thus, for example, when X^4 in general formula (VI) represents a nitro group, or the phenyl group Ar contains a nitro substituent, this may be reduced to a $-NH_2$ group using hydrogen in the presence of a catalyst as previously described for process (1) part (b).

When X^1 in general formula (VI) represents a $-C=O$ group this may be reduced to a $-CH(OH)-$ group using hydrogen in the presence of a catalyst as previously described for process (1) part (b). Alternatively, the reducing agent may be, for example, a hydride such as diborane or a metal hydride such as lithium aluminium hydride, sodium bis(2-methoxyethoxy) aluminium hydride, sodium borohydride or aluminium hydride. The reaction may be effected in a solvent, where appropriate an alcohol e.g. methanol or ethanol, or an ether such as tetrahydrofuran, or a halogenated hydrocarbon such as dichloromethane.

When X^2 in general formula (VI) represents a $-CH_2NY'-$ group or the group $-CH=N-$, or $-X^2-X^3-$ represents $-CH_2N=CR^2X-$ this may be reduced to a $-CH_2NH-$ or $-CH_2NHCHR^2X-$ group using hydrogen in the presence of a metal catalyst as previously described for process (1) part (b). Alternatively, when X^2 or $-X^2-X^3-$ is the group $-CH=N-$ or $-CH_2N=CR^2X-$ this may be reduced to a $-CH_2NH-$ or $-CH_2NHCHR^2X-$ group using a reducing agent and conditions as just described for the reduction of X^1 when this represents a $-C=O$ group.

When X^2 or X^3 in general formula (VI) represents a $-CONH-$ or $-COX-$ group this may be reduced to a group $-CH_2NH-$ or $-CH_2X-$ respectively using a hydride such as diborane or a complex metal hydride such as lithium aluminium hydride or sodium bis(2-methoxyethoxy)aluminium hydride in a solvent such as an ether, e.g. tetrahydrofuran or diethyl ether.

When X^3 represents a group CR^1R^2X where X is C_{2-6} alkenylene or C_{2-6} alkynylene, or Y represents C_{2-4} alkenylene or C_{2-4} alkynylene, this may be reduced to C_{2-6} alkylene or C_{2-4} alkylene respectively using hydrogen in the presence of a catalyst as previously described for process (1) part (b). Alternatively, when X is C_{2-6} alkynylene or Y is C_{2-4} alkynylene this may be reduced to C_{2-6} alkenylene or C_{2-4} alkenylene respectively using for example hydrogen and a lead-poisoned palladium on calcium carbonate catalyst in a solvent such as pyridine, or lithium aluminium hydride in a solvent such as diethyl ether at a low temperature e.g. 0°C.

When Ar is phenyl substituted by a group $-CHO$ or $-CO_2R^9$ where R^9 is hydrogen or alkyl this may be reduced to phenyl substituted by a hydroxymethyl group using for example a complex metal hydride such

as lithium aluminium hydride or sodium borohydride.

In the general processes described above, the compound of formula (I) obtained may be in the form of a salt, conveniently in the form of a physiologically acceptable salt. Where desired, such salts may be converted to the corresponding free acids using conventional methods.

Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting a compound of general formula (I) with an appropriate acid or base in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol, e.g. methanol, ethanol or iso-propanol.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of general formula (I), using conventional methods.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained by resolution of a corresponding racemate of a compound of general formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with the racemate of a compound of general formula (I). The resulting mixture of isomeric salts may be separated for example by fractional crystallisation, into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

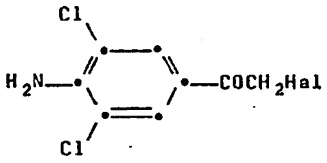
Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Specific diastereoisomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or by conversion of a mixture of isomers of a compound of general formula (I) into appropriate diastereoisomeric derivatives e.g. salts which then can be separated by conventional means e.g. by fractional crystallisation.

Suitable methods for preparing the intermediate compounds used in the above general processes are described below. In the following discussion, Ar, R^1, R^2, R^9, R^{10}, X^1, X^2, X^3, X^4, Y, Y', and L are as defined above except where otherwise indicated. In addition, any substituent in the group Ar may be a precursor substituent which is convertible into the required substituent during the subsequent final-step process. "Hal" represents a halogen atom.

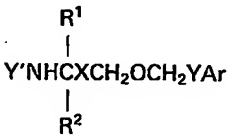
Intermediate compounds of general formula (VI) for use in general process (2) may be prepared by a number of processes.

Thus for example intermediates of general formula (VI) in which X^1 is a group $-C=O$ may be prepared from a haloketone of formula (VII)



(VII)

by reaction with an amine of general formula (VIII)

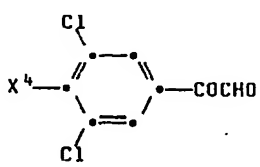


(VIII)

(wherein Y^1 is hydrogen or a group convertible thereto by catalytic hydrogenation). The reaction may be effected in a cold or hot solvent, for example tetrahydrofuran, *tert*-butyl methyl ether, dioxan, chloroform, dimethylformamide, acetonitrile or a ketone such as butanone or methylisobutylketone, or an ester, for example ethyl acetate, preferably in the presence of a base such as diisopropylethylamine, sodium carbonate or other acid scavenger such as propylene oxide.

Intermediates of general formula (VI) in which X^1 is a group $-C=O$ may be reduced to the corresponding intermediate in which X^1 is a group $-CH(OH)-$ using for example a metal hydride such as sodium borohydride in a solvent e.g. ethanol.

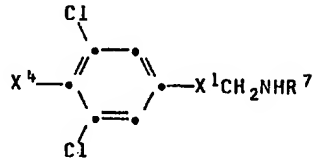
Iminoketones of general formula (VI) i.e. in which X^2 is a group $-CH=N-$ may be obtained from a phenylglyoxal derivative of formula (IX):



(IX)

by reaction with an amine of formula (VIII) in which Y' represents a hydrogen atom in a solvent such as benzene, tetrahydrofuran or an alcohol e.g. ethanol at temperatures up to the reflux. The phenylglyoxal derivatives of formula (IX) may be obtained from a haloketone of formula (VII) by the action of a dialkylsulphoxide such as dimethylsulphoxide.

Intermediates of general formula (VI) in which X^3 is a group $-COX-$ may be prepared by acylation of an amine of formula (X):



(X)

where R^7 is a hydrogen atom using an ester or an activated derivative of an acid of formula (XI):

$$ArYCH_2OCH_2XCO_2H \qquad (XI)$$

Suitable activated derivatives include the acid chloride, an anhydride or imidazolide. The reaction may be optionally carried out in a solvent such as tetrahydrofuran, benzene or chloroform, optionally in the presence of a base such as pyridine or triethylamine. The acids (XI) may be used directly if a coupling agent such as dicyclohexylcarbodiimide is added.

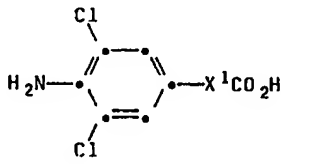
Acids of formula (XI) may be obtained by treatment of an alcohol of general formula (XII)

$$ArYCH_2OCH_2XCH_2OH \qquad (XII)$$

with a suitable oxidising agent, for example pyridinium dichromate in a solvent such as dimethylformamide.

Intermediates of formula (VI) in which $-X^2-X^3-$ represents $-CH_2N=CR^2X-$ may be obtained by reaction of an amine of formula (X) in which R^7 is a hydrogen atom with a compound of formula (IV) in a solvent such as acetonitrile.

Intermediates of formula (VI) in which X^2 is $-CONH-$ may be prepared by reaction of an amine of formula (VIII) in which Y' is a hydrogen atom with an acid of formula (XIII):



(XIII)

in the presence of a coupling agent such as dicyclohexylcarbodiimide. The acids of formula (XIII) may be prepared by methods analogous to conventional methods for the preparation of α-keto- and α-hydroxy carboxylic acids.

Intermediates of formulae (II), (III), (IV) (VII), (VIII) and (XII) are either known compounds or may be prepared by methods analogous to those described for the preparation of known compounds.

Suitable methods for preparing intermediates of formulae (III), (IV), (VIII) and (XII) are described in UK Patent Specification No. 2140800A and in the exemplification included hereinafter.

In addition, for the preparation of ketones of formula (IV) (in which R^2 represents an alkyl group), a halide $ArYCH_2OCH_2XHal$ (where X represents a bond, C_{1-5} alkylene, C_{2-5} alkenylene or C_{2-5} alkynylene) may be reacted with an appropriate β-Ketoester or β-diketone under basic conditions to give an alkylated derivative, which on hydrolysis affords a ketone of formula (IV). The following examples illustrate the invention.

Temperatures are in °C. 'Dried' refers to drying using magnesium sulphate except where otherwise stated. Thin layer chromatography (t.l.c.) was carried out over SiO_2. Flash column chromatography (FCC) was carried out on silica (Merck 9385). The following abbreviations are used:

THF – tetrahydrofuran; EA – ethyl acetate; ER – diethyl ether; CX – cyclohexane; H-hexane; DMF-dimethylformamide; DCM-dichloromethane; TE-triethylamine; ME-methanol; T-toluene; ET-ethanol.

Intermediate 1 referred to below is 1-(4-amino-3,5-dichlorophenyl)-2-bromo-1-ethanone.

Intermediate 2

(a) *1-[2-[(6-Bromohexyl)oxy]ethyl]-4-nitrobenzene*

4-Nitrobenzeneethanol (10.25g), 1,6-dibromohexane (27ml) tetra-n-butylammonium bisulphate (1.7g) and 12.5M aqueous sodium hydroxide (55ml) were stirred together for 40h. The mixture was diluted with water (250ml), extracted with ER (3×350ml) and the combined extracts were washed consecutively with water

(250ml) and brine (250ml), dried and evaporated to give an oil (42.6g). The oil was purified by FCC eluting with ER-CX (0:100->1:19) to give the *title compound* as a yellow oil (9.52g). T.l.c. (ER-CX 1:19) Rf 0.11.

The following compounds were similarly prepared:

(b) *1-[2-[(5-Bromopentyl)oxy]ethyl]-4-methylbenzene*

(17.9g) as a colourless oil, from 4-methylbenzeneethanol (10.0g) and 1,5-dibromopentane (50.7g) with stirring at room temperature for 72h. T.l.c. (ER-CX 1:19) Rf 0.29.

(c) *1-[3-[(5-Bromopentyl)oxy]propyl]-3,5-bis(phenylmethoxy)benzene*

(4.98g) as a colourless oil, from 3,5-bis(phenylmethoxy)benzenepropanol (5.0g) and 1,5-dibromopentane (5.9mℓ) with stirring at room temperature for 16h. T.l.c. (ER-CX 1:19) Rf 0.13.

Intermediate 3

[2-[(5-Bromo-2-pentynyl)oxy]ethyl]benzene

(i) *[2-[(2-Propynyl)oxy]ethyl]benzene*

A mixture of benzenethanol (12.2g), 3-bromo-1-propyne (12.0mℓ), 40% aqueous sodium hydroxide (20mℓ) and tetrabutylammonium bisulphate (1g) was stirred overnight. Water (100mℓ) was added and the mixture was extracted with ER (2×100mℓ). The organic extracts were washed with water and brine, dried and concentrated to a dark oil which was purified by FCC eluting with CX-ER (19:1) to give the *title compound* as a pale yellow oil (12.3g) T.l.c. (CX-ER 19:1) Rf 0.50.

(ii) *5-(2-Phenylethoxy)-3-pentyn-1-ol*

n-Butyl lithium (1.6M in hexane, 35mℓ) was added to a stirred solution of the product of step (i) (8.0g) in dry THF (50mℓ) at −78° under nitrogen. Boron trifluoride etherate (6.8mℓ) was added and the mixture was stirred at −78° for 30 in. Oxirane (7mℓ) was added and the mixture was stirred at −78° for 1h, treated with saturated saturated aqueous ammonium chloride (100mℓ), allowed to warm to room temperature, and extracted with ER (2×100mℓ). The organic extracts were washed with water and brine, dried and concentrated to an orange oil which was purified by FCC eluting with H-ER (2:1) to give the *title compound* as a pale yellow oil (3.95g). T.l.c. (H-ER 2:1) Rf 0.10.

(iii) *[2-[(5-Bromo-2-pentynyl)oxy]ethyl]benzene*

A solution of triphenylphosphine (5.25g) in dry DCM (15mℓ) was added to a solution of the product of step (ii) (3.9g) and carbon tetrabromide (6.63g) in dry DCM (25mℓ) at 0° over 10 min. The yellow solution was stirred at 0° for 30 min, evaporated onto silica (Merck 9385) and purified by FCC eluting with H -> H-ER (3:1) to give the *title compound* as a colourless oil (2.7g). T.l.c. (H-ER 2:1) Rf 0.69.

Intermediate 4

N-[1-Methyl-5-(2-phenylethoxy)pentyl]benzenemethanamine

(i) *6-(2-Phenylethoxy)-2-hexanone*

[2-(4-Bromobutoxy)ethyl]benzene (10.0g) in dry ether (80mℓ) was added dropwise to magnesium turnings (0.946g) under nitrogen with stirring to give a gentle reflux. The reaction mixture was refluxed for 1h, allowed to cool to room temperature and added dropwise to acetic anhydride (8.07g) in dry ether (55mℓ) at −70° under nitrogen with stirring over 1.5h. The reaction mixture was stirred at −70° for 2h, allowed to warm to −10°, then treated with saturated ammonium chloride (100mℓ). The organic layer was separated and the aqueous layer re-extracted with ER (150mℓ). The combined organic extracts were washed with 2N aqueous sodium hydroxide (150mℓ), brine (150mℓ), dried and evaporated to give an oil (7.54g) which was purified by FCC eluting with ER-CX (1:3) to give the *title compound* as a colourless oil (4.34g). T.l.c. (ER-CX 1:3) Rf 0.25.

(ii) *N-[1-Methyl-5-(2-phenylethoxy)pentyl]benzene methanamine*

The product of step (i) (4.16g) and benzylamine (2.03g) in toluene (50mℓ) was refluxed using a Dean-Stark apparatus for 1h. The toluene solution in ethanol (100mℓ) was hydrogenated over pre-reduced 5% platinum oxide on charcoal (0.40g). The reaction mixture was filtered (hyflo) and evaporated to give an oil (5.73g) whih was purified by FCC eluting with EA-CX (1:4) + 1% TE to give the *title compound* as a yellow oil (4.51q). T.l.c. (EA-CX 1:4 + few drops TE) Rf 0.11.

Intermediate 5

2,2,2-Trifluoro-N-[6-[2-[4-(4-morpholinyl)phenyl]ethoxy]hexyl]-N-(phenylmethyl)-acetamide

A solution of Intermediate 13 (10.0g), 2-chloroethyl ether (3.38g), *N,N*-diisopropylethylamine (6.14g) and sodium iodide (7.11g) in DMF (500mℓ) was stirred at 100° for 2 days under nitrogen. The solvent was evaporated and water (200mℓ) was added to the residue. The mixture was extracted with EA (3 × 200mℓ) and the combined dried (Na_2SO_4) extracts were concentrated to give an oil (16.5g) which was purified by FCC eluting with ER-CX (1:2) to give the *title compound* as an orange oil (3.49g). T.l.c. (ER-CX 1:1) Rf 0.26.

Intermediate 6

N-[6-[2-[4-(4-Morpholinyl)phenyl]ethoxy]hexyl]benzenemethanamine

Intermediate 5 (3.25g) in methanol (40mℓ) was stirred under nitrogen for 16h with potassium carbonate (9.0g). More potassium carbonate (4.5g) was added and after 24h water (50mℓ) was added. The mixture was extracted with EA (3 × 50mℓ) and the combined extracts were washed with water (50mℓ) and brine (50mℓ), dried (Na_2SO_4) and concentrated to give the *title compound* as an orange oil (2.59g). T.l.c. (EA + few drops TE) Rf 0.18.

Intermediate 7

N-[4-[2-[[6-[(Phenylmethyl)amino]hexyl]oxy]ethyl]phenyl]acetamide

Acetic anhydride (1.53g) in DCM (25mℓ) was added dropwise to an ice-cooled solution of Intermediate 13 (6.34g) in pyridine (1.19g) and DCM (25mℓ) under nitrogen. After 4h at room temperature the solvent was evaporated and the residual oil in methanol (40mℓ) was stirred under nitrogen with potassium carbonate (9.0g) for 40h, more potassium carbonate (4.0g) being added after 24h. The mixture was diluted with water (100mℓ) and extracted with EA (3 × 100mℓ). The combined extracts were washed with water (100mℓ) and brine (100mℓ), dried (Na_2SO_4) and concentrated to an oil (5.19g) which was purified by FCC eluting with (EA-TE 100:1) to give the *title compound* as an orange oil (2.94g). T.l.c. (EA + few drops TE) Rf 0.15.

Intermediate 8

(a) *N-[6-(2-Phenylethoxy)hexyl]benzenemethanamine*

[2-[(6-Bromohexyl)oxy]ethyl]benzene (4.0g) was added dropwise to benzylamine (20ml) at 110°. The solution was heated at 110-120° for 90 min, cooled, and treated with hydrochloric acid (2M; 125ml). The mixture was extracted with EA (2×100ml) and the extract was washed with aqueous sodium carbonate (100ml) and brine (100ml), dried and evaporated. Distillation of the residue gave the *title compound* as a colourless oil (3.2g) b.p. 180-190°/0.1mmHg. T.l.c. (CX-ER 1:1) Rf 0.25.

(b) *N-[5-(2-Phenylethoxy)pentyl]benzenemethanamine*

(8.6g) was prepared in a similar manner from [2-[(5-bromopentyl)oxy]ethyl]benzene (10g) and benzylamine (30ml). The undistilled product was used without further purification in Example 1(c).

Intermediate 9

(a) *N-[6-[2-(4-Nitrophenyl)ethoxy]hexyl]benzenemethanamine*

Intermediate 2(a) (25.9g) was added dropwise over 40min to benzylamine (60.76g) at 120° (bath). After 2h at 120° the mixture was cooled and water (750ml) and 2N aqueous hydrochloric acid (375ml) were added. The mixture was extracted with EA (3×800ml) and the combined extracts were washed with 2N aqueous sodium carbonate (1ℓ), brine (500ml), dried (Na_2SO_4) and evaporated. The resultant oil (30.4g) was purified by FCC eluting with EA-CX-TE (25:75:1) to give the *title compound* as an orange oil (22.58g). T.l.c. (EA-CX 1:2 with a few drops of TE) Rf 0.33.

The following compound was prepared in a similar manner:

(b) *N-[5-[3-[3,5-bis(phenylmethoxy)phenyl]propoxy]pentyl]benzenemethanamine*, by adding Intermediate 2(c) (2.5g) to benzylamine (4.3mℓ) at 120° under nitrogen with stirring over 5 min, and keeping the reaction mixture at 120° for 4h before pouring into the hydrochloric acid – water mixture. Final purification by FCC eluting with EA-CX (1:2) with a few drops of TE gave the *title compound* as a colourless oil (2.44g). T.l.c. (EA-CX (1:2) + few drops TE) Rf 0.2.

Intermediate 10

(a) *N-[5-[3-(4-Methoxyphenyl)propoxy]pentyl]benzenemethanamine hydrochloride*

1-[3-[(5-Bromopentyl)oxy]propyl]-4-methoxybenzene (2.0g) was added to benzylamine (6mℓ) at 120° under nitrogen. The solution was stirred for 2h at 120° then added (hot) to 2N hydrochloric acid (50mℓ) and water (25mℓ). The resulting precipitate was collected by filtration, washed with 2N hydrochloric acid, water and ER then dried at 50° under vacuum to give the *title compound* as a white solid (1.79g) m.p.118-121°.

The following compound was prepared in a similar manner:

(b) *N-[5-[2-(4-Methylphenyl)ethoxy]pentyl]benzene methanamine hydrochloride* (8.41g) as a white solid, m.p. 138°, from Intermediate 2(b) and benzylamine (20mℓ).

Intermediate 11

N-[5-[2-(4-Fluorophenyl)ethoxy]pentyl]benzenemethanamine hydrochloride

1-[2-[(5-Bromopentyl)oxy]ethyl]-4-fluorobenzene (7.95g) was added dropwise over 10 min to benzylamine (24mℓ) at 125° under nitrogen. The reaction mixture was stirred for 3.5h at 120° and the hot reaction mixture was poured into 2N aqueous hydrochloric acid (170mℓ) and water (220mℓ). After stirring for 15 min the precipitate was collected by filtration to give the *title compound* as a white solid (7.41g) m.p. 112°.

Intermediate 12

1,1-Dimethyl-5-[2-[4-(4-morpholinyl)phenyl]ethoxy]pentanamine

(i) *4-[4-Morpholinyl]benzeneethanol*

4-Aminobenzeneethanol (20.2g), 2-chloroethyl ether (21.1g), *N,N*-diisopropylethylamine (38.1g) and potassium iodide (48.8g) in DMF were heated to 80° under nitrogen for 60h. The solvent was evaporated and the residue (~143g) was purified by FCC eluting with ER-CX (1:1→1:0) to give the *title compound* as a pink-white solid (17.7g) m.p. 57°.

(ii) *4-[4-[2-[(4-Bromobutyl)oxy]ethyl]phenyl]morpholine*

The product of stage (i) (17.6g), 1,4-dibromobutane (30mℓ), 12.5M aqueous sodium hydroxide (100mℓ) and tetra-n-butylammonium bisulphate (2.0g) were stirred rapidly at room temperature for 16H. The mixture was diluted with water (400mℓ), extracted with ER (3×400mℓ) and the combined extracts were washed consecutively with water (400mℓ) and brine (400mℓ), dried and concentrated to give an oil (53.5g) which was

purified by FCC eluting with ER-CX (0.1→1:5) to give the *title compound* as an orange oil (20.1g). T.l.c. ER-hexane (1:5) Rf 0.1.

(iii) *2,2-Dimethyl-6-[2-[4-(4-morpholinyl)phenyl]ethoxy]hexanoic acid*

n-Butyllithium in hexane (1.53M, 113.5mℓ) was added dropwise to *N,N*-diisopropylamine (17.9g) in THF (100mℓ) at −78° under nitrogen. The mixture was warmed to 0°, stirred for 1h and treated dropwise with isobutyric acid (7.65g) in THF (20mℓ). The resulting suspension was stirred at room temperature for 3h, and the product of stage (ii) (20.0g) was added dropwise. The reaction mixture was stirred for 16h at room temperature and the solvent was evaporated. The resultant oil was partitioned between EA (250mℓ) and water (250mℓ). The aqueous layer was acidified to pH6 with 2N aqueous hydrochloric acid and the organic extract was separated. The aqueous layer was extracted with EA (250mℓ) and the combined extracts were concentrated to leave the *title compound* as an orange oil (20.4g). T.l.c. (ER) Rf 0.53.

(iv) *(Phenylmethyl) [5-[2-[4-(4-morpholinyl)phenyl]ethoxy]pentyl]carbamate*

Ethyl chloroformate (3.29g) in acetone (10mℓ) was added dropwise to a solution of the product of stage (iii) (10.0g) and triethylamine (3.0g, 30mmol) in acetone (100mℓ) and water (10mℓ) at 0°. The mixture was stirred at 0° for 40 min and sodium azide (2.0g) in water (25mℓ) was added dropwise. The resulting suspension was stirred at room temperature for 45 min, diluted with water (200mℓ) and extracted with T (2×200mℓ). The dried (Na_2SO_4) extract was heated t 75°-80° for 2.5h and evaporated. The residue was treated with benzyl alcohol (20mℓ), heated at 75°-80° for 60h and benzyl alcohol was removed by distillation (~1mmHg). The resulting oil was purified on a column of silica (Merck 9385) eluted with ER-CX (1:2) to give the *title compound*, as a yellow oil (4.74g). T.l.c. ER-CX (1:2) Rf 0.13.

(v) *1,1-Dimethyl-5-[2-[4-(4-morpholinyl)phenyl]ethoxy]pentanamine*

The product of stage (iv) (7.50g) in ethanol (80mℓ) was hydrogenated over 10% palladium on charcoal (50% paste in water, 1.0g). The reaction mixture was filtered (hyflo) and the solvent was evaporated to give an oil (5.99g) which was purified by FCC eluting with EA-ME-TE (66:33:1) to give the *title compound* as a yellow oil (2.84g). T.l.c. EA-ME-TE (66:33:1) Rf 0.26.

Intermediate 13

N-[6-[2-(4-Aminophenyl)ethoxy]hexyl]-2,2,2-trifluoro-N-(phenylmethyl)acetamide

(i) *2,2,2-Trifluoro-N-[6-[2-(4-nitrophenyl)ethoxy]hexyl]-N-(phenylmethyl)acetamide*

Intermediate 2(a) (5.2g) was added dropwise over 30min to benzylamine (12.25g) at 120° (bath). The mixture was maintained at 120° for 2h, cooled and water (150ml) and 2N aqueous hydrochloric acid (75ml) were added. The mixture was extracted with EA (2×200ml, 1×100ml) and the combined extracts were washed with 2N aqueous sodium carbonate (200ml), brine (200ml), dried (Na_2SO_4) and evaporated to give an oil (5.76g). The oil in DCM (15ml) and TE (2.5ml) was ice-cooled and treated with trifluoroacetic anhydride (2.55ml) in DCM (10ml) over 5min. The reaction mixture was stirred for a further 1h at room temperature. After 64h DCM (20ml) was added and the mixture was washed with 2N aqueous hydrochloric acid (20ml), 8% aqueous sodium bicarbonate (20ml), water (20ml), brine (20ml), dried (Na_2SO_4) and evaporated to give an oil (7.46g), which was purified by FCC eluting with EA-CX-TE (20:80:1) to give *the title compound* as a yellow oil (5.91g). T.l.c. (EA-CX (1:2) + few drops TE) Rf 0.45.

(ii) *N-[6-[2-(4-Aminophenyl)ethoxy]hexyl]-2,2,2-trifluoro-N-(phenylmethyl)acetamide*

A solution of the product of step (i) (4.95g) in ethanol (100ml) was hydrogenated at ambient temperature and pressure over pre-reduced 5% platinum on charcoal (0.5g). The reaction mixture was filtered (hyflo) and evaporated to give an oil (3.79g), which was purified by FCC eluting with EA-CX (1:2) with 1% TE to give *the title compound* as a yellow oil (3.57g). T.l.c. (EA-CX (1:2) + few drops TE) Rf 0.24.

Intermediate 14

N-[5-[2-(4-Methoxyphenyl]ethoxy]pentyl]benzene methanamine hydrochloride

(i) *1-[2-[(5-Bromopentyl)oxy]ethyl]-4-methoxybenzene*

A mixture of 4-methoxybenzeneethanol (7.0g), 1,5-dibromopentane (20mℓ), 50% aqueous sodium hydroxide (30mℓ) and tetrabutylammonium bisulphate (1g) was stirred at room temperature overnight, water (100mℓ) wa added and the mixture was extracted with ER (2×100mℓ). The organic extracts were washed with water and brine, dried and concentrated *in vacuo* to give an oil which was purified by FCC eluting with hexane → hexane-ER (9:1) to give the *title compound* as a colourless liquid (10.5g). T.l.c. hexane-ER (9:1) Rf 0.28.

(ii) *N-[5-[2-(4-Methoxyphenyl]ethoxy]pentyl]benzenemethanamine hydrochloride*

The product of stage (i) (5g) was added to benzylamine (15mℓ) at 140° under nitrogen. After 2h the reaction mixture was poured into 2N hydrochloric (150mℓ) and water (150mℓ). The precipitate was collected by filtration, washed with water and ER then dried under vacuum at 50° to give the *title compound* as a white solid (3.4g) m.p. 123-126°.

Intermediate 15

1-Bromo-6-[(2-propynyl)oxy]hexane, (15.0g) from propargyl alcohol (5.6g) and 1,6-dibromohexane (73.2g) in a similar manner to Intermediate 2a. Purification by FCC eluting with CX followed by CX-ER (19:1). T.l.c. (CX-ER 9:1) Rf 0.4.

Intermediate 16
N-[6-[(2-Propynyl)oxy]hexyl]benzenemethanamine
Intermediate 15 (1.5g) was added dropwise to benzylamine (10mℓ) at 120°. The solution was stirred at *ca* 120° for 1h, cooled, and added to hydrochloric acid (2M; 50mℓ). The mixture was basified with aqueous sodium hydroxide (2M) and extracted with ER (2×200mℓ). The dried extract was evaporated and excess benzylamine was removed under reduced pressure (*ca* 10mℓ). The residue was purified by FCC eluting with ER to give the *title compound* (0.96g). T.l.c. (ER) Rf 0.1.

Intermediate 17
Ethyl 4-[3-[[6-[(phenylmethyl)amino]hexyl]oxy]1-butynyl]benzoate
Ethyl 4-iodobenzoate (4.65g), Intermediate 16 (4.12g), bis(triphenylphosphino)palladium(II)chloride (120mg) and copper (I) iodide (70mg) in diethylamine (90ml) were stirred under nitrogen at room temperature for 16h. ER (100ml) was added and the precipitate was collected by filtration. The filtrate was concentrated and the resultant oil was purified by FCC eluting with ER-TE (100:1) to give the *title compound* as an orange oil (5.96). T.l.c. (ER-TE 100:1). Rf 0.16.

Intermediate 18
Ethyl 4-[3-[[6-[[(4-amino-3,5-dichlorophenyl)2-hydroxyethyl](phenylmethyl)amino]hexyl]oxy]1-propynyl]benzoate
1-(4-Amino-3,5-dichlorophenyl)-2-bromoethanone (3.08g), Intermediate 17 (4.29g), and *N,N*-diisopropylethylamine (1.41g) in THF (50 ml) was left to stand for 16h under nitrogen at room temperature. The precipitate was collected by filtration and the filtrate was concentrated. The resulting oil in ME (60ml) was ice-cooled and treated portionwise with sodium borohydride (1.55g), stirred under nitrogen for 24h and water (200ml) was added. The mixture was extracted with EA (3×150ml) and, the combined extracts were washed with water (200ml) and brine (200ml), dried (Na_2SO_4) and concentrated to give an oil (6.48g) which was purified by FCC eluting with T to give impure *title compound* as a red oil (5.06g). T.l.c. T Rf 0.2.

Example 1
(a) *4-Amino-3,5-dichloro-α-[[[6-[2-(4-nitrophenyl)ethoxy]hexyl][phenylmethyl)amino]methyl]-benzenemethanol*
Intermediate 1 (794mg), Intermediate 9(a) (1.0g) and N,N-diisopropylethylamine (400mg) in THF (15ml) were left at room temperature overnight. The mixture was filtered and the filtrate concentrated *in vacuo* to an oil which was dissolved in methanol (10ml), cooled in an ice-bath, treated with sodium borohydride (200mg) and stirred overnight at room temperature. Water (25ml) was added and the mixture was extracted with EA (3×20ml). The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to an oil which was purified by FCC eluting with CX-EA-TE (80:20:1) to give the *title compound* as an orange oil (1.3g). T.l.c. (CX-EA-TE 80:20:1) Rf 0.21.
The following compounds were prepared in a similar manner:
(b) *4-Amino-3,5-dichloro-α-[[[6-(2-phenylethoxy)hexyl][phenylmethyl)amino]methyl]benzenemethanol* (630mg) as a colourless oil (t.l.c. (CX-EA-TE 80:20:1) Rf 0.23), from Intermediate 1 (500mg) and Intermediate 8(a) (607mg), except that the reaction mixture was decanted from the precipitated needles, which were further washed with ether, before concentrating to an oil, and the reaction with sodium borohydride (100mg) was carried out for only 1h.
(c) *4-Amino-3,5-dichloro-α-[[[5-(2-phenylethoxy)pentyl][phenylmethyl)amino]methyl]benzenemethanol* (690mg) as a colourless oil (t.l.c. (CX-EA-TE 66:33:1) Rf 0.25) from Intermediate 1 (500mg) and Intermediate 8(b) (550mg), allowing the reaction mixture to stand at room temperature for 5h, then adding ER (25ml) before filtering, and evaporating the filtrate. Purification by FCC using CX-EA-TE (66:33:1) as eluent.
(d) *4-Amino-3,5-dichloro-α-[[[6-(4-phenylbutoxy)hexyl][phenylmethyl)amino]methyl]benzenemethanol* (1.37g) as a yellow oil (t.l.c. (EA-CX (1:4) + few drops TE) Rf 0.3) from Intermediate 1 (1.00g), N-[6-(4-phenylbutoxy)hexyl]benzenemethanamine (1.32g) and *N,N*-diisopropylethylamine (0.68ml) in THF (25ml) leaving the reaction mixture for 72h at room temperature under nitrogen, before filtering, and evaporating the filtrate. The resultant residue was dissolved in methanol (20ml) and treated with sodium borohydride (0.267g), stirred under nitrogen at room temperature for 3h and more sodium borohydride (0.108g) was added. After 1h the reaction was worked up by the method of Example 1(a).
(e) *4-Amino-3,5-dichloro-α-[[[1-methyl-5-(2-phenylethoxy)pentyl][phenylmethyl)amino]methyl]-benzenemethanol* (970mg) as a colourless oil (t.l.c. CX-EA-TE (80:20:1) Rf 0.58), from Intermediate 1 (3.1g) and Intermediate 4 (3.4g). Purification by FCC eluting with CX-EA-TE (90:10:1).
(f) *4-Amino-3,5-dichloro-α-[[[5-[2-(4-Fluorophenyl)ethoxy]pentyl][phenylmethyl)amino]methyl]-benzenemethanol* (0.804g) as a colourless oil (t.l.c. (EA-CX-TE 20:80:1) Rf 0:27, from Intermediate 1 (1.00g), Intermediate 11 (1.11g) and *N,N*-diisopropylethylamine (0.912g), except that the reaction mixture was stirred under nitrogen at room temperature for 16h, and the reaction with sodium borohydride was allowed to proceed for only 3h.
(g) *4-Amino-3,5-dichloro-α-[[[6-[2-[4-(4-morpholinyl)phenyl]ethoxy]hexyl][phenylmethyl)amino]methyl]-benzenemethanol* (1.75g) as a viscous oil (t.l.c.H-EA (4:1) Rf 0.11) from Intermediate 1 (1.0g) and Intermediate 6 (1.5g). For treatment with sodium borohydride, the residue was dissolved in ME (40ml) and

THF (10ml) and, following the reaction, the mixture was concentrated to an oil which was partitioned between EA (50mℓ) and water (50mℓ). Final purification by FCC eluting with H-EA (9:1−>4:1).
(h) *N-[4-[2-[[6-[[2-(4-Amino-3,5-dichlorophenyl)-2-hydroxyethyl][phenylmethyl]amino]hexyl]oxy]ethyl]-phenyl]acetamide* (1.13g) as a yellow oil (t.l.c. EA-CX (1:1) + few drops TE Rf 0.2), from Intermediate 1 (1.00g) and Intermediate 7 (1.30g). The sodium borohydride-methanol reaction mixture was stirred under nitrogen for 24h. Final purification by FCC eluting with EA-CX-TE (50:50:1).
(i) *4-Amino 3,5-dichloro-α-[[[5-[2-(4-methylphenyl)ethoxy]pentyl][phenylmethyl]amino]methyl]-benzenemthanol* (0.95g) as a colourless oil (t.l.c. EA-CX-TE (20:80:1) Rf 0.37), from Intermediate 1 (1.00g), Intermediate 10(b) (1.23g) and N,N-diisopropylethylamine (0.912g). The sodium borohydride-methanol reaction mixture was stirred under nitrogen for 48h. Final purification by FCC eluting with EA-CX (1:6) with 1% TE.
(j) *4-Amino-α-[[[5-[3-[3,5-bis(phenylmethoxy)phenyl]propoxy]pentyl][phenylmethyl]amino]methyl]-3,5-dichlorobenzenemethanol* (2.28g) as a yellow oil (t.l.c. EA-CX (1:4) + few drops TE Rf 0.23) from Intermediate 1 (1.0g) and Intermediate 9(b) (1.85g). The sodium borohydride-methanol reaction was allowed to proceed for 24h.
(k) *4-Amino-3,5-dichloro-α-[[[5-[3-(4-methoxyphenyl)propoxy] pentyl][phenylmethyl]amino]methyl]benzenemethanol* (510mg) as a colourless oil (t.l.c. CX-EA (9:1) Rf 0.36) from Intermediate 1 (600mg), Intermediate 10(a) (950mg) and N,N-diisopropylethylamine (650mg). After the sodium borohydride-methanol reaction the mixture was concentrated to an oil and partitioned between water (50mℓ) and EA (50mℓ). Final purification by FCC eluting with CX-EA (9:1).
(l) *4-Amino-3,5-dichloro-α-[[[5-[2-(4-methoxyphenyl)ethoxy]pentyl][phenylmethyl]amino]methyl]-benzenemethanol* (240 mg) as a colourless oil (t.l.c. (hexane-EA-TE 80:20:1) Rf 0.28, from Intermediate 1 (325mg), Intermediate 14 (430mg) and *N,N*-diisopropylethylamine (300mg), except that the reaction with sodium borohydride was carried out for only 6h, after which the solvent was evaporated and the residue was partitioned between 8% aqueous sodium bicarbonate (25mℓ) and ethyl acetate (25mℓ). Purification by FCC using hexane-EA-TE (90:10:1) as eluent. T.l.c. silica (hexane-EA-TE 80:20:1) Rf 0.28.

Example 2
(a) *4-Amino-3,5-dichloro-α-[[[6-(2-phenylethoxy)hexyl]amino]methyl]benzenemethanol*
Example 1(b) (300mg) was hydrogenated over pre-reduced 10% palladium oxide on carbon (50% aqueous paste 40mg) in ethanol (20ml) containing hydrochloric acid 0.6mmol). After 1.5h the catalyst was removed by filtration through hyflo and the filtrate was concentrated *in vacuo*. The residue was dissolved in EA (20ml) and washed with 8% aqueous sodium bicarbonate and brine, dried (Na_2SO_4) and evaporated to an oil. Purification by FCC eluting with EA ME-TE (90:10:1) gave the *title compound* as a white powder (120mg) m.p. 60-63°. T.l.c. (EA-ME-TE 80:20:1) Rf 0.42.
(b) *4-Amino-3,5-dichloro-α-[[[5-(2-phenylethoxy)pentyl]amino]methyl]benzenemethanol*, a cream solid (370mg), m.p. 64-65°, t.l.c. (EA-ME-TE 80:20:1) Rf 0.40 was similarly prepared from Example 1(c) (650mg).

Example 3
4-Amino-α-[[[6-[2-(4-aminophenyl)ethoxy]hexyl]amino]methyl]-3,5-dichlorobenzenemethanol
Example 1(a) (300mg) was hydrogenated over pre-reduced 10% palladium oxide on carbon (50% aqueous paste, 60mg) in ethanol (20ml) containing hydrochloric acid (1:9 conc. HCl/ethanol, 1ml). The catalyst was removed by filtration through hyflo and the ethanol was removed under vacuum. 8% Aqueous sodium bicarbonate (20ml) was added to the residue, which was then extracted with EA (2×20ml). The organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated to a yellow oil which was purified by FCC eluting with EA-ME-TE (80:20:1) to give a solid. Trituration with ER gave the *title compound* as an off-white powder (160mg) m.p. 71-73°. T.l.c. (EA-ME-TE 80:20:1) Rf 0.32.

Example 4
(a) *4-Amino-3,5-dichloro-α-[[[1-methyl-5-(2-phenylethoxy)pentyl]amino]methyl]benzenemethanol*
Example 1(e) (890mg) was hydrogenated over pre-reduced 10% palladium oxide on carbon (50% aqueous paste, 100mg) in ethanol (20mℓ) containing hydrochloric acid (conc. HCl/ethanol, 1:9 v/v, 1.6mℓ). The catalyst was removed by filtration through hyflo and the ethanol was evaporated. The residue was partitioned between 8% aqueous sodium bicarbonate and EA. The aqueous layer was re-extracted with EA and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to give a yellow oil which was purified by FCC eluting with EA-TE (99:1) to yield the *title compound* as a colourless oil (580mg). T.l.c. (EA-TE 99:1) Rf 0.16.
(b) *4-Amino-3,5-dichloro-α-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]benzene methanol* was similarly prepared from Example 1(d) (320mg). Purification by FCC eluting with EA-ME-TE (80:20:1) followed by trituration with dry ER and drying *in vacuo* gave the *title compound* as a white powder (180mg) m.p. 74-76°.
Found: C,63.38;H,7.59;N,6.06;Cl,15.47.
$C_{24}H_{34}Cl_2N_2O_2$ requires C,63.57;H,7.56;N,6.18;Cl,15.64%.

Example 5

4-Amino-3,5-dichloro-α-[[[1,1-dimethyl-5-[2-[4-(4-morpholinyl)phenyl]ethoxy]pentyl]amino]methyl]-benzenemethanol (Z)-butenedioate (salt) 1:1

A solution of 4-amino-3,5-dichloro-α-oxo-benzeneacetaldehyde (1.9g) and Intermediate 12 (2.5g) in benzene (50mℓ) was refluxed in a Dean-Stark apparatus for 1h. The solvent was evaporated, and the residual oil was dissolved in methanol (50mℓ) cooled in an ice-bath and treated portionwise with sodium borohydride (1.5g). The yellow mixture was stirred at room temperature overnight then concentrated to an oil which was partitioned between water (100mℓ) and EA (100mℓ). The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated to an oil which was purified by FCC eluting with T-ET-ammonia (80:20:1) to give a pale yellow oil (2.5g). T.l.c. (T-ET-ammonia 80:20:1) Rf 0.53. A sample of the oil (150mg) in methanol (2mℓ) was treated with a solution of maleic acid (150mg) in methanol (2mℓ). The solvent was removed under vacuum and the residue was triturated with ER to give the *title salt* as a white powder (180mg) m.p. 110-115° (dec).

Analysis Found: C,57.28; H,6.71; N,6.32; Cl,10.83.

$C_{27}H_{39}Cl_2N_3O_3.C_4H_{404}.1/_2H_2O$ requires C,57.32; H,6.83; N,6.47; Cl,10.92%.

Example 6

(a) *4-Amino-3,5-dichloro-α-[[[6-[2-[4-(4-morpholinyl)phenyl]ethoxy]hexyl]amino]methyl]benzenemethanol*

Example 1(g) (1.2g) was hydrogenated over pre-reduced 10% palladium oxide on carbon (50% aqueous paste, 250mg) in ethanol (25mℓ) containing hydrochloric acid (conc. hydrochloric acid/ethanol 1:9 v/v, 2.0mℓ). The catalyst was removed by filtration through hyflo, the ethanol was evaporated and the residue was partitioned between EA (50mℓ) and 8% aqueous sodium bicarbonate (50mℓ). The organic layer was washed with water and brine, dried (Na_2SO_4) and concentrated to a solid which was triturated with ER to give the *title compound* as an off-white powder (820mg) m.p. 102-103°.

Found: C,61.00; H,7.25; N,8.07; Cl,13.65.

$C_{26}H_{37}Cl_2N_3O_3$ requires C,61.17; H,7.31; N,8.23;Cl,13.89%.

(b) *N-[4-[2-[[6-[[2-(4-Amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]hexyl]oxy]ethyl]phenyl]acetamide* (0.60g) as a white solid m.p. 98-100° was similarly prepared from Example 1(h) (1.08g) using pre-reduced 10% palladium on charcoal (100mg) as the catalyst.

Found: C,59.7; H,6.9; N,8.4; Cl,14.6

$C_{24}H_{33}Cl_2N_3O_3$ requires: C,59.8; H,6.9; N,8.7; Cl,14.7%

Example 7

(a) *4-Amino-3,5-dichloro-α-[[[5-[2-[4-(methylphenyl)ethoxy]pentyl]amino]methyl]benzenemethanol*

Example 1(i) (0.92g) was hydrogenated over pre-reduced 10% palladium on charcoal (100mg) in ethanol (20mℓ) containing hydrochloric acid (conc. hydrochloric acid/ethanol, 1:9v/v, 1.62mℓ) and the catalyst was removed by filtration (hyflo). The filtrate was concentrated and the residue was partitioned between EA (50mℓ) and 8% aqueous sodium bicarbonate (2×50mℓ). The organic layer was washed with brine (50mℓ), dried (Na_2SO_4) and concentrated to give an oil (0.7g) which was purified by FCC eluting with EA-TE (100:1) followed by trituration with ether to give the *title compound* as a white solid (0.46g) m.p. 78°-79°.

Found : C,62.2;H,6.9;N,6.5;Cl,16.8.

$C_{22}H_{30}Cl_2N_2O_2$ requires C,62.1;H,7.1;N,6.6;Cl,16.07%.

(b) *4-Amino-3,5-dichloro-α-[[[5-[3-(4-methoxyphenyl)propoxy]pentyl]amino]methyl]benzenemethanol* was similarly prepared from Example 1(k) (450mg) using pre-reduced 10% palladium oxide on carbon (50% aqueous paste, 100mg) as the catalyst. Purification by FCC eluting with T-ET-TE (90:10:1) followed by trituration with dry ER gave the *title compound* as a white solid (150mg) m.p. 63-64°.

Found: C,60.30; H,7.13; N,6.03; Cl,15.74.

$C_{23}H_{32}Cl_2N_2O_3$ requires C,60.66; H,7.08; N,6.15;Cl,15.57%.

(c) *4-Amino-3,5-dichloro-α-[[[5-[2-(4-fluorophenyl)ethoxy]pentyl]amino]methyl]benzenemethanol* was similarly prepared from Example 1(f) (0.783g) using 10% palladium on charcoal (100mg) as the catalyst. Final trituration with hexane gave the *title compound* as a white solid (0.225g) m.p. 75-76°.

Analysis Found: C,59.0; H,6.5; N,6.5; Cl,16.4.

$C_{21}H_{27}Cl_2FN_2O_2$ requires C,58.8; H,6.3; N,6.5; Cl,16.5%.

Example 8

[3-[[5-[[2-(4-Amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]pentyl]oxy]propyl]-1,3-benzendiol

Example 1(j) (2.20g) was hydrogenated over pre-reduced 10% palladium oxide on charcoal (200mg) in ethanol (30mℓ) containing hydrochloric acid (conc. HCl/ET 1:9 v/v 2.75mℓ). The catalyst was removed by filtration (hyflo). The filtrate was concentrated and the residue was partitioned between EA (50mℓ) and 8% aqueous sodium bicarbonate (2×50mℓ). The organic layer was washed with brine (50mℓ) dried (Na_2SO_4) and concentrated to give an oil (1.05g) which was purified by FCC eluting with EA-ME-TE (90:10:1) to give the *title compound* as a white foam (0.369g). T.l.c. (FA-ME-TE 90:10:1) Rf 0.2.

Found: C,57.4; H,6.7; N,5.9; Cl,15.1

$C_{22}H_{30}Cl_2N_2O_4$ requires C,57.8; H,6.6; N,6.1; Cl,15.5%.

Example 9

4-Amino-3,5-dichloro-α-[[[5-(2-phenylethoxy)-3-pentynyl]amino]methyl]benzenemethanol

Intermediate 3 (802mg) in DMF (2mℓ) was added to a stirred solution of 4-amino-α-(aminomethyl)-3,5-dichlorobenzenemethanol (1.0g) and N,N-diisopropylethylamine (650mg) in DMF (20mℓ) at 100° under nitrogen. After 2h the solvent was evaporated and the residue was purified by FCC twice eluting with T-ET-TE (9:5:1) to give a pale yellow oil which was triturated with H to give the *title compound* as a white solid (80mg) m.p. 62.5-63°.

Found: C,61.39; H,5.93; N,6.79; Cl,17.37.

$C_{21}H_{24}Cl_2N_2O_2$ requires C,61.92; H,5.94;N,6.88;Cl,17.41%.

Example 10

4-Amino-3,5-dichloro-α-[[[5-[2-(4-methoxyphenyl)ethoxy]pentyl]amino]methyl]benzenemethanol hydrochloride

Example 1(l) (230mg) was hydrogenated over 10% palladium oxide on carbon (50% aqueous paste, 40mg) in ethanol (10mℓ). The catalyst was removed by filtration through hyflo and the ethanol was evaporated to give a green solid which was triturated with dry ether to give the *title compound* as a pale green powder (170mg) m.p. 134-137° (dec).

Analysis Found: C,54.28; H,6.45; N,5.58; Cl,21.35.

$C_{22}H_{30}Cl_2N_2O_3.HCl.½H_2O$ requires C,54.27; H,6.62; N,5.75; Cl,21.85%.

Example 11

Ethyl 4-[3-[[6-[[(4-amino-3,5-dichlorophenyl)2-hydroxyethyl]amino]hexyl]oxy]propyl]benzoate

Intermediate 18 (500mg) in ET (20ml) containing hydrochloric acid (concHCl 1:9v/v, 0.76ml) was hydrogenated over pre-reduced 10% palladium on charcoal (50% paste in water, 60mg). The reaction mixture was filtered (hyflo) and the filtrate was concentrated. The residue was partitioned between EA (50ml) and 8% aqueous sodium bicarbonate (2×50ml). The organic layer washed with brine (50ml), dried (Na_2SO_4) and concentrated. The residue was purified by FCC eluting with EA-H-TE (50:50:1) to give the *title compound* as a white solid (97mg) m.p. 66-68°. T.l.c. (EA-H-TE 50:50:1) Rf 0.05.

Example 12

4-Amino-3,5-dichloro-α-[[[6-[3-[4-(hydroxymethyl)phenyl]propoxy]hexyl]amino]methyl]benzenemethanol

The compound of Example 11 (88mg) in ER (4ml) was added dropwise to a stirred suspension of lithium aluminium hydride (50mg) in ER (4ml) under nitrogen. The reaction mixture was stirred for 2.5h at room temperature and treated dropwise with water (0.05ml), 2N aqueous sodium sodium hydroxide (0.1ml) and water (0.1ml). The mixture was filtered (hyflo) and the filtrate was concentrated to give a colourless oil (64mg), which on trituration with ER afforded the *title compound* as a white solid m.p. 56-59°. T.l.c. (T-ET-NH_3 39:11:1) Rf 0.44.

The following are examples of suitable formulations of compounds of the invention. The term "active ingredient" is used herein to represent a compound of the invention.

Tablets (Direct Compression)

	mg/tablet
Active ingredient	2.0
Microcrystalline Cellulose USP	196.5
Magnesium Stearate BP	1.5
Compression weight	200.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to microcrystalline cellulose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film forming materials, such as hydroxypropylmethylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Syrup (Sucrose-free)

	mg/5ml dose
Active ingredient	2.0mg
Hydroxypropyl methylcellulose USP (viscosity type 4000)	22.5mg
Buffer) Flavour) Colour) Preservative) Sweetener)	as required
Purified Water BP to	5.0ml

The hydroxypropyl methylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

Metered dose pressurised aerosol

A. Suspension Aerosol

	mg/metered dose	*Per can*
Active ingredient micronised	0.100	26.40mg
Oleic Acid BP	0.100	2.64mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is mixed with the Trichlorofluoromethane at a temperature of 10-15°C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves delivering 85mg of suspension are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

B. Solution Aerosol

	mg/metered dose	*Per can*
Active ingredient	0.055	13.20mg
Ethanol BP	11.100	2.66g
Dichlorotetrafluoroethane BP	25.160	6.04g
Dichlorodifluoromethane BP	37.740	9.06g

Oleic acid BP, or a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included.

The active ingredient is dissolved in the ethanol together with the oleic acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the dichlorotetrafluoroethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

Injection for intravenous administration

		mg/ml
	Active ingredient	0.5mg
	Sodium Chloride BP	as required
	Water for Injection BP to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

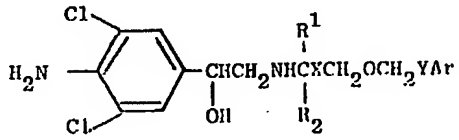
Inhalation cartridges

		mg/cartridge
Active ingredient micronised		0.200
Lactose BP	to	25.0

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler.

CLAIMS

1. Compounds of the general formula (I)



(I)

wherein

X represents a C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain and

Y represents a bond, or a C_{1-4} alkylene, C_{2-4} alkenylene or C_{2-4} alkynylene chain with the proviso that the sum total of carbon atoms in X and Y is not more than 8;

Ar represents a phenyl group optionally substituted by one or more substituents selected from halogen atoms, or the groups C_{1-3} alkyl, C_{1-3} alkoxy, $-(CH_2)_qOH$ (where q represents an integer from 0 to 3), $-NR^3R^4$ (where R^3 and R^4 each represents a hydrogen atom, or a C_{1-4} alkyl group, or NR^3R^4 forms a saturated heterocyclic amino group which has 5-7 ring members and optionally contains in the ring one or more atoms selected from $-O-$ or $-S-$ or a group $-NH-$ or $-N(CH_3)-$), or $-NR^5COR^6$ (where R^5 represents a hydrogen atom or a C_{1-4} alkyl group, and R^6 represents a hydrogen atom or a C_{1-4} alkyl, C_{1-4} alkoxy, phenyl or $-NR^3R^4$ group), or Ar is a phenyl group substituted by an alkylenedioxy group of formula $-O(CH_2)_pO-$, where p is 1 or 2;

R^1 and R^2 each represents a hydrogen atom or a C_{1-3} alkyl group, with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4; and physiologically acceptable and solvates thereof.

2. Compounds as claimed in claim 1, in which the chain X is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2C\equiv C-$, $-(CH_2)_2CH=CH-$, $-(CH_2)_2C\equiv C-$, $-CH=CHCH_2-$, $-CH=CH(CH_2)_2-$ or $-CH_2C\equiv CCH_2$ and the chain Y is $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH=CH-$, $-C\equiv C-$, $-CH_2CH=CH-$ or $-CH_2C\equiv C-$.

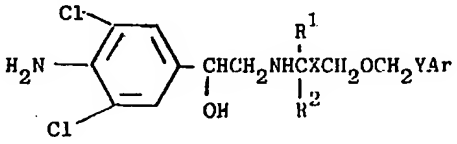
3. Compounds as claimed in claim 1, in which X is a C_{2-6} alkylene or C_{2-6} alkynylene chain and Y is a C_{1-4} alkylene chain.

4. Compounds as claimed in any of claims 1 to 3 in which R^1 and R^2 independently represent a hydrogen atom or a methyl group.

5. Compounds as claimed in any of claims 1 to 3, in which R^1 and R^2 are both hydrogen atoms or R^1 is a hydrogen atom and R^2 is a C_{1-3} alkyl group.

6. Compounds as claimed in any of claims 1 to 5, in which Ar is an unsubstituted phenyl group or is a phenyl group having one, two or three substituents selected from bromine, iodine, chlorine, fluorine, methyl, ethyl, methoxy, ethoxy, amino, methylamino, ethylamino, dimethylamino, diethylamino, morpholino, piperidiono, piperazino, N-methylpiperazino, $-NHCOR^6$ (where R^6 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, phenyl or amino), hydroxyl, $-CH_2OH$, or $-(CH_2)_2OH$.

7. Compounds of the general formula (Ia),



(Ia)

wherein

X represents a C_{3-4} alkylene or C_3 alkynylene chain;

Y represents a C_{1-3} alkylene chain;

R^1 and R^2 each represent hydrogen or methyl; and

Ar represents a phenyl group optionally substituted by a fluorine atom, a group selected from amino, C_{1-3} alkyl, C_{1-3} alkoxy, hydroxyC_{1-2}alkyl, morpholino, hydroxy or $-NHCOR^6$ where R^6 is C_{1-3} alkyl, or Ar is a phenyl group substituted by hydroxyl groups at the 3- and 5- positions; and physiologically acceptable salts and solvates thereof.

8. Compounds as claimed in claim 7 in which Ar is a phenyl group optionally containing one substituent at the 4- position, which is an amino, $-NHAcetyl$ or morpholino group.

9. The compounds:

4-amino-3,5-dichloro-α-[[[6-[2-[4-(4-morpholinyl)-phenyl]ethoxy]hexyl]amino]methyl]benzenemethanol;

N-[4-[2-[[6-[[2-(4-amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]hexyl] xy]ethyl]pentyl]acetamide;

4-amino-3,5-dichloro-α-[[[6-[2-(4-aminophenyl)ethoxy]-hexyl]amino]methyl]benzenemethanol;

4-amino-3,5-dichloro-α-[[[5-(2-phenylethoxy]pentyl]-amino]methyl]benzenemethanol;

4-amino-3,5-dichloro-α-[[[6-(2-phenylethoxy)hexyl]amino]methyl]benzenemethanol;

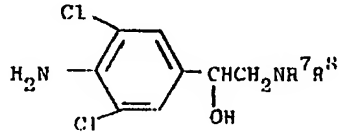
4-amino-3,5-dichloro-α-[[[1-methyl-5-(2-phenylethoxy)-penyl]amino]methyl]benzenemethanol;

4-amino-3,5-dichloro-α-[[[5-(2-phenylethoxy)-3-pentynyl]amino]methyl]benzenemethanol;

[3-[[5-[[2-(4-amino-3,5-dichlorophenyl)-2-hydroxyethyl]amino]pentyl]oxy]propyl]-1,3-benzenediol; and physiologically acceptable salts and solvates thereof.

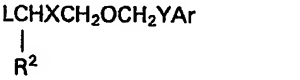
10. A process for the preparation of compounds as claimed in any of claims 1 to 9 or a physiologically acceptable salt or solvate thereof which comprises:

(Ia) for the preparation of compounds of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (II)



(II)

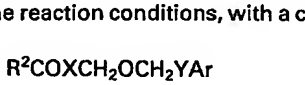
(wherein R^7 is a hydrogen atom or a protecting group and R^8 is a hydrogen atom) with an alkylating agent of general formula (III)



(III)

(where L is a leaving group) followed, if necessary, by removal of any protecting groups present; or

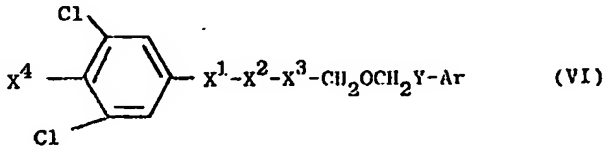
(Ib) for the preparation of compounds of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (II) in which R^7 is a hydrogen atom or a protecting group and R^8 is a hydrogen atom or a group convertible thereto under the reaction conditions, with a compound of general formula (IV)



(IV)

in the presence of a reducing agent followed, if necessary, by removal of any protecting group present; or

(2) reducing an intermediate of general formula (VI)



(VI)

wherein

X^1 is $-CH(OH)-$ or a group convertible thereto by reduction, X^2 is $-CH_2NR^7-$ or a group convertible thereto by reduction. X^3 is $-CR^1R^2X-$ or a group convertible thereto by reduction, X^4 is $-NH_2$ or a group convertible thereto by reduction, Y is as defined in claim 1 or is a group convertible thereto by reduction and Ar is as defined in claim 1 or is a group convertible thereto by reduction,

at least one of X^1, X^2, X^3, X^4, Y and Ar containing a reducible group, followed, if necessary, by removal of any protecting groups present; and

if desired, converting the resulting compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

11. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in any of claims 1 to 9 or a physiologically acceptable salt or solvate thereof, together with a physiologically acceptable carrier or excipient.

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